Attorney Docket No. 6443.500-US
Hansen et al.
Serial No. 10/699,338 Filed October 31, 2003

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CLAIM LISTING

1. **(Cancelled)**

2. **(Currently amended)** A method for treating a disorder, disease or condition benefiting from an increase in mitochondrial respiration**; wherein the disorder, disease or condition is selected from the group consisting of obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, and cancer** ~~**in a patient in need thereof**~~ comprising administering **to a patient in need thereof** a therapeutically effective amount of a compound having a slope calculated from the equation

$$X^n = (Y_2-Y_0)/(Y_1-Y_0)$$

wherein

$Y_0$ is the degree of stimulation measured as counts per minute (cpm) **of radioactivity** ~~**in Assay (I)**~~ in control samples without added test compound,

and

$Y_1$ is the degree of stimulation measured as cpm **of radioactivity** ~~**in Assay (I)**~~ with added test compound in a concentration of $EC_{50}/2$,

$Y_2$ is the degree of stimulation measured as cpm **of radioactivity** ~~**in Assay (I)**~~ with added test compound in concentration of $2xEC_{50}$, and

X is 2,

or

$Y_1$ is the degree of stimulation measured as cpm **of radioactivity** ~~**in Assay (I)**~~ with added test compound in a concentration of $EC_{50}/3$,

$Y_2$ is the degree of stimulation measured as cpm **of radioactivity** ~~**in Assay (I)**~~ with added test compound in concentration of $3xEC_{50}$, and

X is 3,

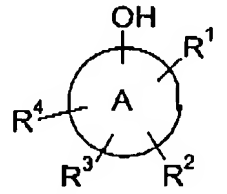
and

n is the slope,

**wherein,**

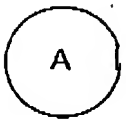
**the value of the slope n calculated for the compound is ~~of a value~~** less than the value **~~for~~ of** the slope **n** calculated **~~from the above equation with~~ for** carbonylcyanide *p*-trifluoromethoxy-phenylhydrazone as test compound **~~in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof~~; and**

**wherein the compound is of formula (I)**




**(I)**

**wherein**




**is an aryl, or heteroaryl,**

**$R^1$ is halogen, -CHO, $-CO_2R^{32}$, $-COR^{32}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, -CH=CH-$R^{33}$, $-C(R^{33})(R^{34})$, $-SOR^{32}$, $-SO_2R^{32}$ or aryl substituted with from one to five substituents selected from halogen, -CHO, $-CO_2R^{32}$, $-COR^{32}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, -CH=CH-$R^{33}$, $-CH(R^{33})(R^{34})$, $-SOR^{32}$, or $-SO_2R^{32}$, wherein**

**$R^{32}$ is hydrogen, alkyl, aryl, or heteroaryl; and**

**$R^{33}$ and $R^{34}$ independently of each other are halogen, -CHO, $-CO_2R^{35}$, $-COR^{35}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-SOR^{35}$, $-SO_2R^{35}$, wherein**

**$R^{35}$ is hydrogen or alkyl;**

**and is attached on a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;**

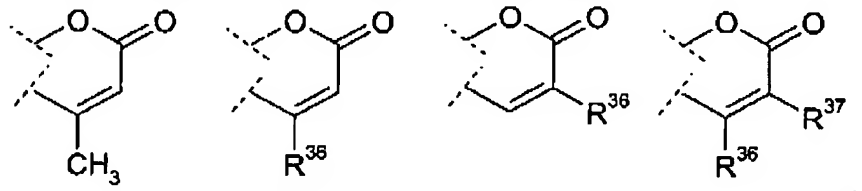
**$R^2$ is $C(X)_3$, $NO_2$, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl, wherein**

**X is halogen; and**

$R^3$ and $R^4$ independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

$R^2$ and $R^3$ together form one of the diradicals



wherein

$R^{36}$ and $R^{37}$, independently of each other, are hydrogen, halogen, $C(X)_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl, wherein

X is halogen;

and wherein the two valence atoms in the diradical are attached to adjacent carbon atoms; and

$R^4$ is hydrogen, halogen, $C(X)_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

3. **(Cancelled)**

4. **(Cancelled)**

5. **(Currently amended)** A method according to claim 2 [[4]], wherein the condition is obesity.

6. **(Currently amended)** A method according to claim 2 [[4]], wherein the disease is type 2 diabetes.

7. (Original) A method according to claim 6, wherein the patient in need thereof is obese.

8. **(Withdrawn)** A method according to claim 4, wherein the disease is dyslipidemia.

9. **(Withdrawn)** A method according to claim 8, wherein the patient in need thereof is obese.

10. **(Cancelled)**

11. **(Withdrawn/Currently amended)** A method for treating a disorder, disease or condition benefiting from a reduction of reactive oxygen species **wherein the disorder, disease or condition to be treated is selected from the group consisting of the aging process, damage to heart tissue, damage to endothelial cells, damage to neuronal tissue, Alzheimer's disease, cancer, cataract, diabetic microvascular diseases in the retina, renal glomerus and peripheral nerve cell apoptosis** ~~in a patient in need thereof~~ comprising administering **to a patient in need thereof** a therapeutically effective amount of a compound having a slope calculated from the equation

$$X^n = (Y_2-Y_0)/(Y_1-Y_0)$$

wherein

$Y_0$ is the degree of stimulation measured as counts per minute (cpm) **of radioactivity** ~~in Assay (I)~~ in control samples without added test compound,

and

$Y_1$ is the degree of stimulation measured as cpm **of radioactivity** ~~in Assay (I)~~ with added test compound in a concentration of $EC_{50}/2$,

$Y_2$ is the degree of stimulation measured as cpm **of radioactivity** ~~in Assay (I)~~ with added test compound in concentration of $2xEC_{50}$, and

X is 2,

or

$Y_1$ is the degree of stimulation measured as cpm in **of radioactivity** ~~Assay (I)~~ with added test compound in a concentration of $EC_{50}/3$,

$Y_2$ is the degree of stimulation measured as cpm in **of radioactivity** ~~Assay (I)~~ with added test compound in concentration of $3xEC_{50}$, and

X is 3,

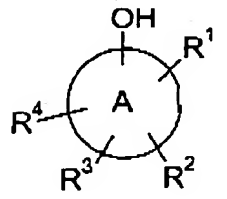
and

n is the slope,

**wherein,**

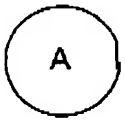
**the value of the slope n calculated for the compound is ~~of a value~~** less than the value **~~for~~ of** the slope **n** calculated **~~from the above equation with~~ for** carbonylcyanide *p*-trifluoromethoxy-phenylhydrazone as test compound **~~in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof~~; and**

**wherein the compound is of formula (I)**




**(I)**

**wherein**




**is an aryl, or heteroaryl,**

**$R^1$ is halogen, -CHO, $-CO_2R^{32}$, $-COR^{32}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{33}$, $-C(R^{33})(R^{34})$, $-SOR^{32}$, $-SO_2R^{32}$ or aryl substituted with from one to five substituents selected from halogen, -CHO, $-CO_2R^{32}$, $-COR^{32}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{33}$, $-CH(R^{33})(R^{34})$, $-SOR^{32}$, or $-SO_2R^{32}$, wherein**

**$R^{32}$ is hydrogen, alkyl, aryl, or heteroaryl; and**

**$R^{33}$ and $R^{34}$ independently of each other are halogen, -CHO, $-CO_2R^{35}$, $-COR^{35}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-SOR^{35}$, $-SO_2R^{35}$, wherein**

**$R^{35}$ is hydrogen or alkyl;**

**and is attached on a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;**

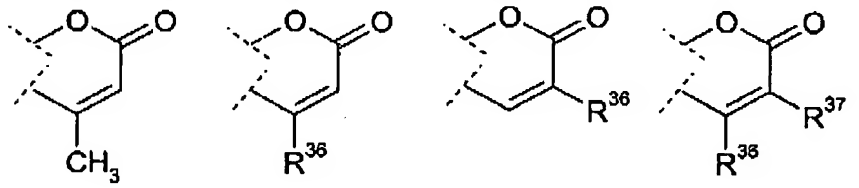
**$R^2$ is $C(X)_3$, $NO_2$, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl, wherein**

**X is halogen; and**

**$R^3$ and $R^4$ independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;**

**or**

**$R^2$ and $R^3$ together form one of the diradicals**



**wherein**

**$R^{36}$ and $R^{37}$, independently of each other, are hydrogen, halogen, $C(X)_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl, wherein**

**X is halogen;**

**and wherein the two valence atoms in the diradical are attached to adjacent carbon atoms; and**

**$R^4$ is hydrogen, halogen, $C(X)_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl;**

**or a pharmaceutically acceptable salt, solvate or prodrug thereof.**

12. **(Cancelled)**

13. **(Cancelled)**

14. **(Currently amended)** A method according to claim 2 ~~1~~, wherein the compound is a chemical uncoupler ~~as defined in Assay (II), as described in the specification~~.

15. **(Currently amended)** A method according to claim 2 ~~1~~, wherein the compound is a cation.

16. **(Cancelled)**

17. **(Currently amended)** A ~~a~~ method according to claim 2 ~~16~~, wherein the compound is selected from **the group consisting of:**

4-methoxy-2-nitrophenol,

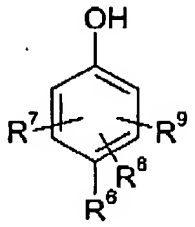
4-hydroxy-3-nitroacetophenone, **and** ~~**or**~~

7-hydroxy-4-methyl-8-nitro-chromen-2-one.

18. **(Cancelled)**

19. **(Cancelled)**

20. **(Withdrawn/Currently amended)** A method according to claim 2, ~~1~~ wherein the compound is of ~~**the general**~~ formula (III)




(III)

wherein

$R^6$ is halogen, -CHO, $-CO_2R^{43}$, $-COR^{43}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{44}$, $-C(R^{44})(R^{45})$, $-SOR^{43}$, $-SO_2R^{43}$ or aryl substituted with from one to five substituents selected from halogen, -CHO, $-CO_2R^{43}$, $-COR^{43}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{44}$, $-CH(R^{44})(R^{45})$, $-SOR^{43}$, or $-SO_2R^{43}$, wherein

$R^{43}$ is hydrogen or alkyl; and

$R^{44}$ and $R^{45}$ independently of each other are halogen, -CHO, $-CO_2R^{46}$, $-COR^{46}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-SOR^{46}$, $-SO_2R^{46}$, wherein

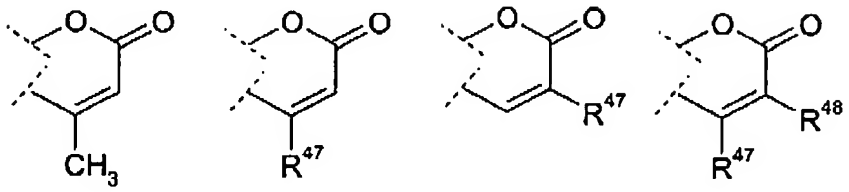
$R^{46}$ is hydrogen, alkyl, or aryl;

$R^7$ is alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-; and

$R^8$ and $R^9$ independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

$R^7$ and $R^8$ together ~~**forms**~~ **form one of** the diradicals



wherein $R^{47}$ and $R^{48}$, independently of each other, are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-,

wherein the two valence atoms **in the diradical** are ~~connected~~ **attached** to adjacent carbon atoms **in the phenyl ring**; and

$R^9$ is hydrogen, alkyl, nitro, halogen, alkyl-O-, or alkyl-C(O)- ;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

21.-43. **(Cancelled)**

44. **(New)** A method according to claim 2, wherein the cancer is selected from the group consisting of endometrial cancer, breast cancer, prostate cancer, and colon cancer.

45. **(New)** A method according to claim 11, wherein the cancer is selected from the group consisting of endometrial cancer, breast cancer, prostate cancer, and colon cancer.

46. **(New)** A method according to claim11, wherein the compound is a chemical uncoupler.

47. **(New)** A method according to claim 11, wherein the compound is a cation.

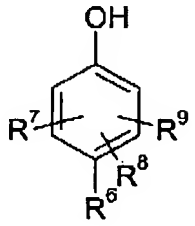
48. **(New)** A ~~a~~ method according to claim 11, wherein the compound is selected from the group consisting of:

4-methoxy-2-nitrophenol,

4-hydroxy-3-nitroacetophenone, and

7-hydroxy-4-methyl-8-nitro-chromen-2-one.

49. (New) A method according to claim 11, wherein the compound is of formula (III)



(III)

wherein

$R^6$ is halogen, -CHO, $-CO_2R^{43}$, $-COR^{43}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{44}$, $-C(R^{44})(R^{45})$, $-SOR^{43}$, $-SO_2R^{43}$ or aryl substituted with from one to five substituents selected from halogen, -CHO, $-CO_2R^{43}$, $-COR^{43}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-CH=CH-R^{44}$, $-CH(R^{44})(R^{45})$, $-SOR^{43}$, or $-SO_2R^{43}$, wherein

$R^{43}$ is hydrogen or alkyl; and

$R^{44}$ and $R^{45}$ independently of each other are halogen, -CHO, $-CO_2R^{46}$, $-COR^{46}$, $-SO_3H$, $-CCl_3$, $-CF_3$, -NO, $-NO_2$, -CN, $-SOR^{46}$, $-SO_2R^{46}$, wherein

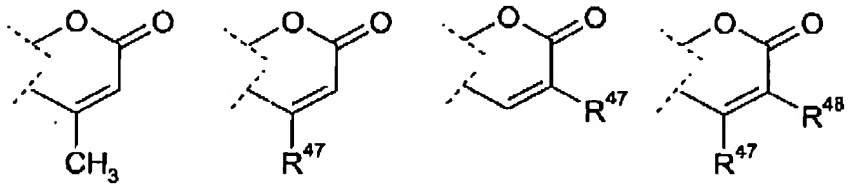
$R^{46}$ is hydrogen, alkyl, or aryl;

$R^7$ is alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-; and

$R^8$ and $R^9$ independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

$R^7$ and $R^8$ together form one of the diradicals



wherein $R^{47}$ and $R^{48}$, independently of each other, are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-,

wherein the two valence atoms in the diradical are attached to adjacent carbon atoms in the phenyl ring; and

$R^9$ is hydrogen, alkyl, nitro, halogen, alkyl-O-, or alkyl-C(O)-;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.